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Special Article

Palliative thoracic radiotherapy in lung cancer: An American Society for Radiation Oncology evidence-based clinical practice guideline

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Abstract

Purpose: To provide guidance to physicians and patients with regard to the use of external beam radiotherapy, endobronchial brachytherapy, and concurrent chemotherapy in the setting of palliative thoracic treatment for lung cancer, based on available evidence complemented by expert opinion.

Methods and Materials: A Task Force authorized by the American Society for Radiation Oncology (ASTRO) Board of Directors synthesized and assessed evidence from 3 systematic

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reviews on the following topics: (1) dose fractionation in thoracic external beam radiotherapy (EBRT); (2) clinical utility of initial and salvage endobronchial brachytherapy (EBB); and (3) use of concurrent chemotherapy (CC) with palliative thoracic radiotherapy. Practice guideline recommendations were produced and are contained herein.

Results: Studies suggest that higher dose/fractionation palliative EBRT regimens (eg, 30 Gy/10 fraction equivalent or greater) are associated with modest improvements in survival and total symptom score, particularly in patients with good performance status. As these improvements are associated with an increase in esophageal toxicity, various shorter EBRT dose/fractionation schedules (eg, 20 Gy in 5 fractions, 17 Gy in 2 weekly fractions, 10 Gy in 1 fraction), which provide good symptomatic relief with fewer side effects, can be used for patients requesting a shorter treatment course and/or in those with a poor performance status. No defined role for EBB in the *routine* initial palliative treatment of chest disease has been demonstrated; however, EBB can be a reasonable option for the palliation of endobronchial lesions causing obstructive symptomatology including lung collapse, or for hemoptysis after EBRT failure. The integration of concurrent chemotherapy with palliative intent/fractionated radiotherapy is not currently supported by the medical literature.

Conclusion: This Guideline is intended to serve as a guide for the use of EBRT, EBB, and CC in thoracic palliation of lung cancer outside the clinical trial setting. Further prospective clinical investigations with relevant palliative endpoints into the respective roles of EBB and CC/targeted therapy in the thoracic palliation of lung cancer are warranted, given the current state of the medical literature in these areas.

Introduction

Many patients with metastatic lung cancer (LC), and selected patients with locally advanced disease, are routinely treated with thoracic radiotherapy with palliative intent to relieve tumor-related symptoms (hemoptysis, bronchial obstruction, cough, shortness of breath, and chest pain) and to improve health-related quality of life (QoL).[1] The majority of randomized controlled trials and meta-analyses/systematic reviews have focused on the questions of external-beam radiation therapy (EBRT) dose fractionation and the use of endobronchial brachytherapy (EBB) in the initial or salvage palliative management (either alone or in conjunction with other treatment modalities) of lung cancer. In addition, the use of concurrent chemotherapy (CC) with palliative radiotherapy has been the subject of various investigations. Practice guidelines and consensus statements have been previously prepared to provide guidance to practitioners and patients with regard to treatment options.[1-8] In addition, investigations into treatment selection from the practitioner,[9] patient,[10] and economic viewpoints[11] have been undertaken to provide guidance.

Given the issues regarding the heterogeneity of therapeutic approaches for the thoracic palliation of LC with radiotherapy, the American Society for Radiation Oncology (ASTRO) Clinical Affairs and Quality Committee convened a Task Force of experts in the field of LC to develop a guideline on the use of radiotherapy in the thoracic palliation of LC with EBRT, EBB, and CC with radiotherapy. Guideline recommendations, contained herein, were based on the results of a systematic review of the literature and supplemented by the expert opinion from the members of the Task Force.

Methods and materials

Process

In conjunction with an ongoing international palliative LC workshop consensus project,[12] the Guidelines Subcommittee of the ASTRO Clinical Affairs and Quality Committee (CAQC) identified the use of palliative radiotherapy as it is applied to LC as a high-priority topic needing an evidence-based guideline. Accordingly, a project proposal to the ASTRO Board of Directors was prepared by 2 ASTRO members of the international palliative lung workshop consensus working group (G. Rodrigues and B. Movsas) and was approved in June 2009. The Board of Directors authorized creation of a TF to study issues related to the use of radiotherapy in the treatment of LC and approved its membership, which included 7 recognized experts in LC radiation oncology, 1 in radiation oncology/pulmonology/community practice, 1 representative from the Guidelines Subcommittee of the CAQC, 1 medical oncologist, and 1 radiation oncology resident.

The TF was to review and synthesize currently available evidence to develop a clinically practical, evidence-based guideline to help radiation oncologists and LC patients to determine the appropriate use of EBRT, EBB, and concurrent palliative chemoradiotherapy for palliative intent LC patients. The members of the Task Force divided into 3 subgroups to address separate questions based upon

their particular areas of expertise. Through a series of communications by conference calls and e-mail, the TF completed the systematic literature review, reviewed manuscripts, created evidence tables, and formulated the practice guidelines contained herein. The initial draft of the manuscript was reviewed by 3 expert reviewers (see Acknowledgment) and then ASTRO legal counsel, and was subsequently placed on the ASTRO Web site (during the month of December 2010) for a period of public comment. Upon integration of this feedback, the document was then submitted to the ASTRO Board of Directors for their final review and approval in January 2011. The TF sought to adhere to the American Medical Association's Physician Consortium for Performance Improvement guidance for measure development and recent calls for reform of the guideline process during the preparation of this practice guideline.[13,14] The ASTRO Guidelines Subcommittee will monitor this guideline and initiate an update when appropriate.

Literature search

A literature search strategy was developed around the 3 practice guideline questions of EBRT dose fractionation, indications for EBB, and use of CC with palliative intent radiotherapy. All search strategies were performed on PubMed assessing possible articles from 1966 to March 1, 2010. In particular, identification of randomized controlled trials (RCTs) or of other prospective clinical trial evaluations, if RCTs were unavailable, was the focus of the literature search. Reference lists for published practice guidelines, consensus statements, metaanalyses, and systematic reviews were cross-referenced with search strategies to ensure a complete set of manuscripts and abstracts for review by the TF. All abstracts were initially reviewed by GR for an assessment of study relevance before a formal collection of manuscripts/abstracts for TF review and data synthesis. The following key words and MeSH headings were used for the respective research questions: (1) What is the optimal dose/fractionation schedule for thoracic EBRT in patients with lung cancer? (radiotherapy/radiation, dosage/dose fractionation, palliative, quality of life, lung neoplasms, clinical trial, metaanalysis, RCT, and review, 174 articles); (2) What is the role of EBB alone or in conjunction with other modalities (including external beam radiation) in both the initial and salvage palliative management of lung cancer? (lung neoplasms, brachytherapy, palliative, clinical trial, metaanalysis, practice guideline, RCT, 21 articles); and (3) What is the role of chemotherapy administered concurrently (chemotherapy drug delivery on same days for some or all radiation fractions) with radiation for the palliation of lung cancer? (antineoplastic combined chemotherapy protocols/agents, palliation, lung neoplasms, radiation/radiotherapy, chemoradiation/chemoradiotherapy, 109 articles).

Results

What is the optimal dose/fractionation schedule for thoracic palliative EBRT in patients with LC?

Guideline statement

Since 1985, multiple prospective randomized trials of different dose/fractionation schedules have shown that thoracic palliative EBRT can alleviate thoracic symptoms in patients with locally advanced or metastatic non–small cell lung cancer (NSCLC) who are not candidates for curative therapy. Studies suggest that higher dose/fractionation EBRT regimens (eg, 30-Gy/10-fraction equivalent or greater) are associated with modest improvements in survival and total symptom score, primarily in patients with good performance status. As these improvements are also associated with a increase in side effects or adverse effects, such as radiation esophagitis, various shorter fractionation schedules (eg, 20 Gy in 5 fractions, 17 Gy in 2 weekly fractions, 10 Gy in 1 fraction) have been demonstrated to provide good symptomatic control with fewer side effects, and can be used for patients requesting shorter treatment courses and/or with poor performance status.

Narrative

Patients requiring palliative thoracic RT present with symptoms that are caused by locoregional growth of tumor that may be safely and adequately encompassed by an RT field. Indications for thoracic EBRT include, but are not limited to: hemoptysis, cough, chest pain, dyspnea, obstructive pneumonia, dysphagia related to esophageal compression, superior vena cava syndrome, hoarseness, or stridor. Symptoms caused by malignant pleural effusion, lymphangitic carcinomatosis, and multilobar parenchymal disease typically are not suitable for palliative thoracic EBRT.

There have been 14 RCTs[15-28] published to date addressing the question of the optimal EBRT dose schedule to palliate symptomatic advanced LC. A comprehensive review of these trials was completed in 2006[4] and updated in 2009[29] with no change in conclusions, by the Cochrane Collaboration. A total of 3708 patients were randomized in the 14 trials, and of these 3576 were evaluable. Descriptive features of these trials are provided in Table 1.

Overall, the 14 studies were heterogeneous by the dose regimens used, the performance status, the age of patients accrued, and the selection and reporting of outcomes, leaving the Cochrane group able to perform a narrative synthesis only. Significant heterogeneity of symptom assessment and toxicity endpoints were observed; however, in general, all studies showed a beneficial effect of the palliative RT, without any specific schedule being favored. In the studies that conducted QoL analyses (XRT),[24-26] there were no major differences noted between schedules.

Table 1 Randomized controlled trials assessing palliative lung radiotherapy fractionation

Study	Y	Radiotherapy schedules compared	Evaluable patients (n)	Survival [a] by regimen (P = NS unless specified)	Symptom control by regimen (P = NS unless specified)
Simpson	1985	40 Gy/20 F daily continuous/4 wk vs 30 Gy/10 F/2 wk vs 40 Gy/10 F/4 wk, split course	316	6.2 mo vs 6.9 mo vs 6.4 mo	No difference
Teo	1988	45 Gy/18 F/3.5 wk vs 31.2 Gy/4 F/4 wk	273	20 wk vs 20 wk	Better with 45 Gy, P = .012
MRC	1991	30 Gy/10 F/2 wk or 27 Gy/6 F/2 wk or 17 Gy/2 F/8 d	369	177 d vs 179 d	No difference
MRC	1992	17 Gy/2 F/8 d vs 10 Gy/1 fraction	235	100 d vs 122 d	No difference
Abratt	1995	35 Gy/10 F/2.5 wk vs 45 Gy/15 F/3.75 wk	84	8.5 mo vs 8.5 mo	No difference
MRC	1996	36 or 39 Gy/12 or 13 F/2.5 wk vs 17 Gy/2 F/8 d	509	1. 9 mo vs 2.7 mo, P = .03	No difference
Rees	1997	17 Gy/2 F/8 d vs 22.5 Gy/5 F/5 d	216	23% vs 18% (1 y)	No difference
Reinfuss	1999	50 Gy/25 F/5 wk (conventional) vs 40 Gy/10 F daily (split course with 4 wk gap) vs delayed radiotherapy (20–25 Gy/4 or 5 F when symptomatic).	240	18% vs 6% vs 0%, P < .05 (2 y)	No assessment of symptoms
Nestle	2000	32 Gy/16 F twice daily/10 d vs 60 Gy/30 F/6 wk	152	36% vs 38% (1 y)	No difference
Bezjak	2002	20 Gy/5 F/1 wk vs 10 Gy/1 F	230	6 mo vs 4.2 mo, P = .03	Better for 20 Gy on Lung Cancer Symptom Scale, P = .009
Sundstrom	2004	17 Gy/2 F/8 d vs 42 Gy/15 F/3 wk vs 50 Gy/25 F/5 wk	407	6.8 mo vs 7.0 mo vs 8.2 mo	No difference
Erridge	2005	30 Gy/10 F/2 wk vs 10 Gy/1 F	148	23 wk vs 28 wk	Better for 30-Gy arm, P = .05
Kramer	2005	30 Gy/10 F/2 wk vs 16 Gy/2 F/8 d	297	20% vs 11%, P = .03 (1 y)	No difference
Senkus-Konefka	2005	20 Gy/5 F/1 wk vs 16 Gy/2 F/8 d	100	5.3 mo vs 8.0 mo, P = .016	No difference

F, fraction; Gy, gray; NS, nonsignificant.
[a] Survival given as median value or percentage at specific timepoint.

With respect to toxicity, although it was reported as generally mild for the majority of patients in all studies, a consistent finding was that higher-dose regimens were associated with increased toxicity, particularly esophagitis. Late toxicity in the form of radiation myelopathy, although rare, was noted in 4 trials.[17,18,20,25] Seven trials that described response endpoints found no differences between regimens.[15-17,19,22,23,28] Overall the Cochrane conclusions were as follows: (1) there was no strong evidence favoring 1 EBRT schedule over another with respect to efficacy of palliation; (2) acute toxicity was greater with higher-dose regimens; (3) patients with better performance status might have a survival benefit with the higher dose regimens (5% at 1 year and 3% at 2 years); and (4) radiation myelopathy may be associated with some regimens (eg, 17 Gy/2 fractions), requiring appropriate RT planning. A 2008 review[30] and a recent 2010 review[31] have arrived at similar conclusions.

Fairchild et al[30] carried out a quantitative pooling of data abstracted from each study's text, figures, and tables. They reported a statistically higher survival and lower total symptom score with the higher dose schedules (30 Gy/10 fractions equivalent or higher—eg, 30–35 Gy/10 fractions, 36–45Gy/12–15 fractions [3 Gy/day], or 50–60 Gy/25–30 fractions [2 Gy/day]), at the cost of increased esophageal toxicity. Of interest, Macbeth and Stephens[32] grouped 13 of 14 trials by radiobiological equivalency (RBE), comparing the following: (1) RBE-equivalent regimens in all groups of patients; (2) RBE-equivalent regimens in patients with poor performance status; and (3) RBE-differing regimens in better performance status patients. For group 1, the investigators found similar efficacy and survival irrespective of radiation regimen. For group 2, they concluded that a single 10-Gy fraction is an effective and suitable treatment. For group 3, they found only 1 study[16] with any significant differences in symptom control, and 2 trials[20,22] with significantly better survival for high dose (30-Gy/10-fraction equivalent or greater) radiation regimens.

In summary, the clinical trial evidence has demonstrated that higher dose radiation treatment fractionations (30-

Gy/10-fraction equivalent or greater) are associated with improvements in total symptom score and survival (but at the cost of some increased side effects, such as radiation esophagitis), primarily in patients with good performance status. The specific high-dose fractionation schedule to optimize the therapeutic ratio between improvements in total symptom score/survival and minimization of normal tissue effects such as radiation esophagitis is currently unknown. Similarly, the impact of newer treatment technologies such as intensity-modulated radiation therapy (IMRT), image-guided radiation therapy (IGRT), as well as the integration of pretreatment imaging (eg, ^{18}fluorodeoxyglucose–positron emission tomography [^{18}FDG-PET]) in the context of thoracic palliative radiation therapy has not yet been clearly defined. These dose fractionation and technology considerations should be explored in future prospective clinical trials of patients receiving palliative lung radiotherapy.

Various shorter fractionation schedules (eg, 20 Gy in 5 fractions, 17 Gy in 2 fractions, and 10 Gy in 1 fraction) also provide good symptomatic relief and can be used for patients requesting shorter total treatment courses and also for patients with poor performance status. In addition, in the setting of patients actively receiving palliative chemotherapy with new thoracic symptoms, shorter fractionation schedules may be more easily integrated between chemotherapy cycles without chemotherapy delays for patients with thoracic symptomology that could benefit from thoracic radiotherapy.

What is the role of EBB alone or in conjunction with other modalities (including EBRT) in both the initial and salvage palliative management of LC?

Guideline statement

There is currently no randomized or metaanalysis-based evidence to recommend EBB alone or in conjunction with other palliative therapies (EBRT, chemotherapy, Nd:YAG laser) in the *routine* initial palliative management of endobronchial obstruction resulting from LC. If there is already evidence of collapsed lung resulting from central endobronchial disease, initial EBB in conjunction with EBRT can be considered because of observed increased reexpansion rates in a randomized clinical trial. EBB also remains a reasonable option in the palliative management of a patient with endobronchial lesion causing obstruction or hemoptysis who has previously received thoracic EBRT. Continuing prospective clinical trials in the areas of initial and salvage EBB are encouraged to better define the role of this modality in the palliation of LC patients.

Narrative

In some patients with LC, it is possible to treat a tumor in the bronchus through the placement of endobronchial catheters. This allows delivery of radiation to the luminal aspect of the tumor and, thereby, opening of the bronchial obstruction. The goal of such therapy is the relief of endobronchial symptoms such as cough, shortness of breath, and hemoptysis. EBB cannot be used to treat extrabronchial disease or disease in the lung parenchyma.

The literature search identified 6 RCTs (Table 2) that have evaluated the palliative role of EBB in LC.[32-39] One matched pair analysis[40] and an additional RCT[41] were reported in the context of radical dose external beam radiotherapy. These 2 additional studies did not report on any palliative endpoints and therefore were not considered further in this practice guideline.

Mallick et al[33] randomized 45 patients with non–small cell lung cancer (NSCLC) into 3 treatment arms. Arm A patients received EBRT of 30 Gy/10 fractions and EBB of 16 Gy/2 fractions at 1 cm, delivered once weekly. Arm B received EBRT of 30 Gy/10 fractions and EBB to 10 Gy/1 fraction at 1 cm. Arm C received no EBRT and EBB of 15 Gy/1 fraction at 1 cm. When analyzed by groups, there were no differences in response rates for dyspnea, cough, or hemoptysis; however, the study may have been underpowered to answer these questions.

Sur et al[34,35] reported the results of an RCT on inoperable Stage III NSCLC patients who were not suited for chemoradiation treatment and who had luminal disease. Initially patients were treated with EBRT of 30 Gy/10 fractions, 36 Gy/18 fractions, or 40 Gy/20 fractions, at the discretion of the treating physician. Patients were randomized to receive 2 EBB treatments of 6 Gy/fraction at 1 cm, delivered once weekly (Group A) or EBRT of 20 Gy/10 fractions (Group B). The improvement in quality of life was similar in both groups, although duration of symptom-free survival was shorter with EBB (median 77 days for EBB vs 129 days for EBRT, $P = .009$).

Langendijk et al[36] randomized 95 patients with endobronchial NSCLC to receive EBRT alone (arm 1) or EBRT and EBB (arm 2). Patients receiving EBRT either received a radical (60 Gy) or palliative (30 Gy) radiation dose, at the discretion of the treating physician. Patients in arm 2 received EBB of 15 Gy/2 fractions at 1 cm, delivered once weekly. The median survival was similar for the 2 groups (8.5 months for EBRT alone, and 7 months for EBRT plus EBB, $P = .21$). Rates of lung re-expansion, defined radiographically or spirometrically, were improved with EBB (35% for EBRT alone vs 57% for EBRT plus EBB, $P = .01$). Correspondingly, a temporary improvement in the palliation of patient-reported dyspnea was noted with the addition of EBB to EBRT over EBRT alone ($P = .02$). This study suggested that EBB with EBRT may be used in selected patients with severe dyspnea resulting from endobronchial tumor obstruction in the main bronchus.

Chella et al[37] randomized 29 patients with NSCLC involving the central airway and not eligible for surgery, chemotherapy, or EBRT. Fifteen patients (group 1) had

Table 2 Randomized controlled trials assessing endobronchial brachytherapy

Author	Y	Disease description	Patient no.	Treatment	Median FU	Survival [a]	Symptom endpoints	Complications
Mallick	2006	Untreated inoperable stage III NSCLC with endobronchial disease	15	EBRT 30 Gy/10F+HDREB 8 Gy @ 1 cm q1w × 2	6 mo	NR	No significant differences in dyspnea, cough, or hemoptysis reported	FH n = 1
			15	EBRT 30Gy/10F+HDREB 10Gy @ 1 cm × 1	6 mo	NR		
			15	HDREB 15 Gy @ 1 cm × 1	6 mo	NR		
Sur	2002	Inoperable, stage III proven NSCLC, luminal disease, no prior treatment	65	All patients: EBR: 30 Gy/10 F; or 36 Gy/18 F; or 40 Gy/20 F followed by either:	12		No significant differences in dyspnea, cough, or hemoptysis reported	NR
	2004		NR	EBRT: 20 Gy/10 F over 2 wk; or	12	29.4% (1 y)		
			NR	HDREB: 12 Gy/2 F over 2 wk @ 1 cm Mean HDREB dose: NR	12	29.7% (1 y) P = NS		
Langendijk	2001	Inoperable stage IIIB NSCLC with tumor in main or lobar bronchus	47	Radical EBRT (60 Gy) or palliative EBRT (30 Gy)	NR	8.5 mo (95% CI = 5.4–11.6)	Temporary improvement in patient-reported dyspnea for HDREB arm	FH 13%
			48	Radical or palliative EBRT + HDREB of 7.5Gy @ 1 cm q1w × 2 Mean HDREB dose: NR	NR	7.0 mo (95% CI = 5.3–8.9) P = NS	P = .02	FH 15% P = NS
Chella	2000	NSCLC involving central airway, SQ 72%	15	Nd-YAG: 25–45 W using pulses up to 1.2 s to a mean total of 1850 J	17.8	NR	Mean symptom-free survival increased from 2.8 to 8.5 mo by addition of HDREB	0%
			14	Nd-YAG + HDREB of 5 Gy @ 0.5 cm q1w × 3 Mean HDREB dose: NR			P < .05	7%
Stout	2000	Inoperable, histologically proven NSCLC, SQ 82%	50	EBRT: 30 Gy/8 F over 10–12 d	NR	9.4 mo/38% (1 y)	Improved symptom palliation for EBRT (83%) vs HDREB (59%)	6%
			49	HDREB: 15 Gy @ 1 cm × 1 Mean HDREB dose: NR		8.2 mo/22% (1 y) P = .04	P = .03	8%
Huber	1995	Histologically proven stage I–IV lung cancer, IIB/IV 80%, SQ 49%	44	HDREB (4): 3.8 Gy @ 1 cm q1w × 4	30	4.2 mo/11.4% (1 y)	No significant differences in dyspnea, cough, or hemoptysis reported	22%
			49	HDREB (2): 7.2 Gy @ 1 cm q3w × 2 Mean HDREB dose: HDREB (4)/(2), 13.4 ± 5.2 Gy/13.7 ± 4.4 Gy		4.4 mo/20.4% (1 y) P = NS		21%

CI, confidence interval; EBRT, external beam radiotherapy; FH, fatal hemopytsis; HDREB, high-dose-rate endobronchial brachytherapy; Gy, gray; F, fraction(s); J, joule; Nd-YAG, neodymium-doped yttrium: aluminium garnet; NR, not reported; NSCLC, non–small cell lung cancer; pts, patients; SQ, squamous histology.

[a] Survival reported either as median value or as percentage at specific time point.

laser debulking only, whereas 14 patients (group 2) had laser debulking followed by EBB. The EBB was given 15 to 18 days after neodymium-doped yttrium:aluminium garnet (Nd-YAG) to a dose of 15 Gy/3 fractions at 0.5 cm, delivered once weekly. The mean duration of symptom-free and progression-free survival increased from 2.8 to 8.5 months and 2.2 to 7.5 months favoring EBB, respectively ($P < .05$, each).

Stout et al[38] randomized 99 untreated patients with stage III NSCLC and symptoms of endobronchial obstruction to EBB of 15 Gy/1 fraction (49 patients) at 1 cm or EBRT 30 Gy/8 fractions (50 patients). A statistically significant improvement in overall survival and patient-reported symptom palliation was seen for EBRT vs EBB (1-year survival 37% vs 22%, $P = .04$; 83% palliation vs 59%, $P = .03$).

Huber et al[39] performed an EBB dose optimization study in 93 patients primarily with advanced LC. Group 1 received EBB of 15.4 Gy/4 fractions at 1cm, delivered weekly. Group 2 received EBB of 14.4 Gy/2 fractions at 1 cm, delivered over a 3-week interval. There were no significant differences between the groups in terms of local control, fatal hemopytsis, or 1-year overall survival. The study did not evaluate relief of symptoms or QoL.

In total, there are only 426 patients represented on the aforementioned studies, with no individual RCT having sufficient numbers to draw definite conclusions. It is evident that the addition of EBB does not improve survival for patients with LC (Table 2). In fact, the only trial reviewed that reports a significant difference in survival for LC patients between EBRT and EBB favors EBRT.[38] A recent Cochrane systematic review of 13 RCTs came to similar conclusions: EBRT is superior to EBB for the initial palliation of symptoms, and there is no added benefit to EBRT plus EBB over EBRT alone[7] or with EBB versus EBRT and Nd-YAG laser. These findings are likely due to the fact that EBRT is indicated in most cases because of extrabronchial bulky disease that cannot be addressed with EBB. In addition, a bronchoscopic procedure is performed for catheter placement as part of an EBB procedure. At the time of this procedure, the lesion can be debulked/bypassed with ablative procedures and/or stenting and, in all cases, must be opened to pass the EBB catheter. These procedures would tend to reduce or eliminate the usefulness of integrating EBB with EBRT.

EBB remains a reasonable therapeutic maneuver, when feasible, in patients who would have failed previous EBRT and now present with recurrent bronchial obstruction or hemoptysis and/or in selected patients presenting with initial lung obstruction in the setting of nonmetastatic endobronchial disease. The goal of the EBB in the latter group would be to potentially re-expand the lung before or in conjunction with radical dose radiotherapy, if clinically appropriate. No ideal EBB dose prescription regimen was identified in the literature with regard to these 2 clinical scenarios (salvage therapy after EBRT and initial lung obstruction with nonmetastatic disease). Further prospective clinical trials defining the specific indications/criteria for use of EBB and the optimal dose fractionation prescription regimens to be used are encouraged.

What is the role of chemotherapy administered concurrently with radiation for the palliation of LC?

Guideline statement

At this time, there is no added benefit for the use of chemotherapy concurrently with radiation therapy (RT) in the palliation of thoracic symptoms in lung cancer patients. To date, there is 1 randomized phase III study directly addressing this issue.[42] This study showed that, although the addition of chemotherapy to RT increased the overall response rate, this small benefit came at the cost of significant increased toxicity with no significant improvement in overall survival, progression-free survival, or symptom palliation. Most of the remainder of the studies have been early phase I studies involving a heterogeneous group of patients with a paucity of prospective quality of life data. In the context of patients receiving palliative chemotherapy, the goal should be to optimally sequence or integrate courses of chemotherapy and RT in a nonconcurrent fashion to palliate lung symptoms as clinically indicated. The use of concurrent chemoradiation should primarily be reserved for clinical trials.

Narrative

Recently, systemic chemotherapy has become a standard of care for patients with metastatic or recurrent NSCLC. Several randomized studies have demonstrated that, when compared with best supportive care (BSC), chemotherapy not only significantly improves survival but also reduces symptoms and enhances QoL. Moreover, in 1 study comparing chemotherapy to BSC, significantly fewer patients randomized to chemotherapy required palliative radiation (49% vs 79%), and the median time to radiation was significantly delayed in the chemotherapy arm (29 weeks vs 4 weeks).[43] At the same time, in patients with locally advanced NSCLC, intact PS, and limited weight loss, several RCTs have shown an advantage for the use of concurrent chemoradiation over sequential therapies.[44,45] These studies demonstrated an improvement in overall survival, presumably due to the synergistic effects of combining chemotherapy and radiation, but at the cost of increased toxicity particularly severe esophagitis. In light of these concerns, it is reasonable to study the benefit/risk ratio of adding chemotherapy concurrently with thoracic radiation in the palliative setting for LC. A MEDLINE search identified several prospective studies that address this issue[42,46-53]; these studies are summarized in Table 3.

Table 3 Prospective clinical trials assessing concurrent chemotherapy with palliative lung radiotherapy

First author	Year	Phase	Stage [a]	N	RT	Chemo	MS (mo)	CR/PR	Gr 3 + NH toxicity/QOL	Comment
Ball	1997	III	"Advanced"	200	20 Gy/5 F	± FU 1 mg/m^2/d × 5 d	6 (RT) vs 6.8 (chemo-RT) P = .36	Overall response 29% vs 16% P = .035	Increased toxicity with chemo (N/V, esophagitis [12% vs 3%], stomatitis, skin reaction)	Randomized study Studied QOL No significant difference in OS, DFS, or palliation
Micheal	2005	I	IIIB/IV	24	40 Gy/20 F	Dose escalated weekly PV to V = 30 mg/m^2; P = 20 mg/m^2	13.5	4%/61%	No gr 3+ esophagitis or lung Significant decrease in cough on LCSS	PET response 89% infield Has QOL (LCSS)
Hoffman	2002	I	II/III/IV	36	2 Gy/d x 5–7 wk	V 15 mg/m^2 d 1, 8 q 3 wk × 2 C AUC 1.5 escalated to AUC 3	13.5	17%/52%	22% esophagitis 11% Lung (8% gr 5)	~25% severe NH toxicity (8% gr 5 toxicity)
Siewert	2007	I	III/IV	30	40–66 Gy	Prem 200–600 mg/m^2 q 21 d × 2 or Prem 500 mg/m^2 + escalating C (AUC 4–6) q 21 d × 2	NA	7%/27%	7% esophagitis	Preparation for stage III study
Jeremic	1999	II	IV	50	14 Gy/2 F (d 1, 8)	C 300 mg/m^2 d 1, 29 etoposide 50 mg/m^2 d 1–21 and d 29–42	7	6%/21%	19% esophagitis 9% lung (6% improvement in symptoms)	"Elderly" (>70 y)

(*continued on next page*)

Table 3 (*continued*)

First author	Year	Phase	Stage[a]	N	RT	Chemo	MS (mo)	CR/PR	Gr 3 + NH toxicity/QOL	Comment
Schwarzenberger	2004	I	III/IV	26	5 Gy/wk x 10	Dose-escalated docetaxel 10 mg/m^2/wk – 45 mg/m^2/wk	17	5%/68%	No gr 3 esophagitis or lung	Full dose taxane Excellent response (promising MS) Limited toxicity
Choi	2008	I	Progressive/ recurrent	14	30 Gy/10 F	Dose escalated G 40–65 mg/m^2 2 × 1 wk	6	0%/43%	7% esophagitis	MTD is G 50 mg/m^2 2X/wk
Silvano	2000	I	IIIB/IV	29	17 Gy/2 F/1 per wk or 60 Gy/12 F/1 per wk	V 20–30 mg/m^2 d 1, 8, q21 × 6 V 10–20 mg/m^2/wk × 12	NA	NA	3% esophagitis 6% gr 5	MTD with 17 Gy is V 20 mg/m^2 MTD with 60 Gy is V 10 mg/m^2

AUC, area under the curve; C, carboplatin; Chemo, chemotherapy; CR, complete response; DFS, disease-free survival; F, fraction; gr, grade; MTD, maximal tolerated dose; MS, median survival; NA, not available; N, number of patients; LCSS, lung cancer symptom scale; NH, nonhematologic; N/V, nausea/vomiting; OS, overall survival; P, cisplatin; PR, partial response; Prem, premetrexed; QoL, quality of life; V, vinorelbine.

[a] Almost all "unsuitable for radical RT".

There are several limitations regarding the data available. The majority of these studies are early phase I (safety) studies, with relatively small numbers of patients. At this time, there appears to be only 1 RCT focusing on this issue[42]; however, this RCT used fluorouracil, an agent currently not commonly used in systemic therapy in LC. A second challenge relates to the degree of patient heterogeneity included in these prospective studies. There is variation in the staging procedures used, patient stage, performance status, degree of weight loss, age, and gender. There is considerable variation regarding the actual treatments administered, both with respect to RT (dose and schedule), as well as chemotherapy (type, dose, and schedule). Some of the studies used a hypofractionated palliative radiation approach (14–17 Gy/2 fractions), whereas others used high doses of radiation over approximately 6 to 7 weeks.[47,48] The systemic agents, dosing, and timing used varied considerably among studies. Another major limitation in most studies is the absence of routine patient-reported symptom or QoL instruments for assessment of the palliative response.

Despite these limitations, careful review of these studies demonstrates some important lessons. There has been only 1 large RCT (n = 200).[42] Patients received 20 Gy/5 fractions and were randomized either to thoracic RT alone or to RT plus fluorouracil (1 g/m^2/day for 5 days by continuous infusion). Eligibility stipulated a diagnosis of NSCLC with disease "unsuitable for either attempted curative resection or radical RT or recurrent intrathoracic cancer outside any previously radiated volume." The overall radiographic response rate was higher in RT plus fluorouracil (29% vs 16%, $P = .035$). However, there was no significant improvement in disease-free survival, overall survival, or palliation of symptoms. Rather, patients treated with combined modality therapy had significantly more acute toxicity, including nausea and vomiting ($P = .01$), esophagitis ($P = .0003$), stomatitis ($P = .0005$), and skin reactions ($P = .003$). There were no significant differences between the 2 arms in any of the thoracic symptoms or QoL scales. Although the improved radiographic response suggests an interaction between radiation and fluorouracil in NSCLC, this combination did not translate into better palliation.

Other smaller (typically phase I) studies also question the relative benefit versus the risk of adding chemotherapy concurrently with RT for the palliation of LC. Hoffman et al[47] designed a phase I study to determine the maximal tolerated dose of carboplatin when administered in combination with a fixed dose of vinorelbine and concurrent RT in patients with advanced NSCLC. EBRT was administered in daily fractions of 2 Gy over 5 to 7 weeks. With respect to toxicity, 8 of 36 treated patients (22%) had severe (grade 3/4) esophagitis. Of even more concern, 4 patients developed pneumonitis 4 to 7 months after completing therapy, which was fatal in 3 patients. Overall, approximately 25% of patients developed severe

nonhematologic toxicity, and 8% had grade 5 toxicity. In this study, the overall radiological response rate was 52% and the median survival was 13.5 months. By comparison, in a larger study of 240 patients with stage III disease who were "also unsuitable for a radical RT approach," Reinfuss et al reported a similar (12-month) median survival using RT (50 Gy/25 fractions) without any chemotherapy.[49] Similarly, Jeremic et al[50] studied 50 "elderly" patients (>70 years) with stage IV NSCLC who were treated with a combination of 14 Gy/2 fractions concurrently with carboplatin (200 mg/m^2 days 1 and 29 and etoposide 15 mg/m^2 on days 1–21 and 29–42). In this study, there was a 19% rate of grade 3 esophagitis and a 9% rate of grade 3 lung toxicity. Median survival was 7 months and the overall response rate was 27%. As previously pointed out, without a comparison arm, it is difficult to evaluate whether there is a benefit to this combined approach compared with radiation or chemotherapy alone, yet there does appear to be an increase in the rate of toxicity.

Moreover, there are virtually no data for more "modern" chemotherapy typically used in the new millennia, such as premetrexed, as well as taxanes. However, some lessons are available by extrapolation:

1. Bevacizumab in combination with XRT is unwise and unproved. The Southwestern Oncology Group (SWOG) has suspended a trial attempting to integrate this agent into full dose radiation, in combination with etoposide and cisplatin, in part because of the possibility of excess hemoptysis and other life-threatening complications. In limited SCLC, the addition of bevacizumab to standard chemoradiation has led to tracheal–esophageal fistulas.[54]
2. Gemcitabine is a potent radiosensitizer with marked mimetic effect, with reports of severe esophagitis and pneumonitis.[55]
3. In a CALGB study in poor-risk patients receiving definitive RT after induction chemotherapy, the addition of gefitinib to RT does not seem to exacerbate in-field toxicities. This approach yielded a median survival of nearly 20 months.[56]

Overall, studies to date have suggested that the benefit/risk ratio does not support the addition of chemotherapy concomitantly with radiation for the palliation of LC, primarily because of concerns regarding toxicity and no clear evidence that symptom palliation is improved. It is possible, though, that optimization of the radiation technique and attention to the nature and schedule of systemic therapy may, in the future, improve the therapeutic benefit. For example, Schwarzenberger et al[51] studied 26 patients with advanced NSCLC (stage III/IV) who were treated with hypofractionated RT (5 Gy per week × 10) concurrently with dose escalated docetaxel (10–45 mg/m^2 per week). The RT technique used a "field within a field" approach in which the gross tumor volume received 3 Gy per fraction and the clinical target value 2 Gy per fraction. With this approach, the investigators were able to fully escalate the dose of the chemotherapy with limited toxicity. There were no grade 3/4 nonhematologic toxicities among 19 evaluable patients. Moreover, the investigators observed an excellent response rate involving 14 of 19 (74%) evaluable patients, 3 of whom subsequently underwent surgery and were downstaged to stage I. The median survival in this study was also promising at 17 months. The chemotherapy agent of the study was administered 24 hours before the RT fraction to take advantage of the "peak sensitizing effect." Although this was an early phase I study with the limitations noted above, it suggests that novel approaches may exist to combine standard chemotherapy (and newer biological agents) and radiation in this setting to enhance the therapeutic ratio. Thus, although there is no proven role for combining chemotherapy concurrently with RT for palliation of LC, this strategy requires further study and could potentially become a promising approach in the future to help optimize the risk/benefit ratio. It is critical that validated QoL measures be included in such studies since the primary goal of these studies is palliation. At this time, the standard of care in the palliation of LC remains chemotherapy alone and/or thoracic radiotherapy alone without concurrent chemotherapy. However, the goal should be to optimally sequence and integrate the courses of chemotherapy and RT to palliate lung symptoms as clinically indicated. Use of concurrent chemoradiation should primarily be reserved for clinical trials.

Conclusion

The medical literature suggests that patients with good performance status may benefit from higher-dose/fractionation EBRT palliation (30-Gy/10-fraction equivalent or greater) because of the observed modest observed survival benefit. No defined role for endobronchial brachytherapy for the routine initial palliative treatment of chest disease has been demonstrated; however, endobronchial brachytherapy remains an option for the palliation of endobronchial lesions causing obstructive symptomatology in the EBRT failure scenario or in locally advanced nonmetastatic cancer patients with endobronchial disease who require lung re-expansion before or in conjunction with radical RT. The integration of concurrent chemotherapy with palliative intent/fractionated RT is not currently supported by the medical literature. However, integration of palliative chemotherapy and RT in a nonconcurrent fashion is important for the optimal palliation of lung cancer patients with thoracic symptoms. Recent (and ongoing) changes in pretreatment lung cancer imaging, systemic agents, and radiation planning/delivery technologies (eg, IMRT, IGRT, and stereotactic body RT) will require continued prospective evaluation to optimize

patient clinical and health-related QoL outcome in this patient population.

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This Guideline was prepared on the basis of information available at the time the Task Group was conducting its research and discussions on this topic. There may be new developments that are not reflected in this Guideline, and that may, over time, be a basis for ASTRO to consider revisiting and updating the Guideline.

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